functional variants thereof, said functional variants (i) comprising at least 6 amino acid residues, (ii) having at least 70% homology with all of the peptide of SEQ. ID No. 1 and (iii) retaining said calcium channel modulatory function of the peptide of SEQ. ID No.1 and having no cholinesterase activity.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Initially, Applicants and their undersigned representative wish to express their sincere appreciation to the Examiners for their courtesy and helpful suggestions made during the personal interview.

In addition, in support of the remarks contained herein below, a Declaration has been submitted along with the response under 37 CFR 1.132.

The specification has been carefully reviewed and editorial changes have been effected. The changes to the specification are minor and non-substantive in nature and therefore do not require extensive discussion.

Claim 13 has been amended to more particularly define the present invention and to put the claims in better form under U.S. practice. Support for the claim amendments is readily apparent from the teachings of the specification and the original claims.

With regard to the restriction requirement, Applicants respectfully request the Examiner to reconsider her restriction requirement in light of the following comments. The Examiner has

withdrawn claims 34-38 since the Examiner believes that these claims do not relate to a single general inventive concept under PCT Rule 13.1 and because, under PCT Rule 13.2, the claims lack the same or corresponding special technical feature. However, Applicants believe that the Examiner is mistaken in this regard.

Applicants submit that if claims 34-38 were introduced at the international examination stage before the European Patent Office, they certainly would not have generated an equivalent lack of unity objection. The European Patent Office would have found that there is no distinction between the method of claim 33 and the method of claim 34. Both of these claims are linked to claim 13 by virtue of the fact that they specify particular uses of the claimed peptides. Claims 35 and 36 are merely directed to different embodiments of the screening method of claim 34 which respectively, specifically identify a compound with the desired calcium channel modulatory function and incorporate such compound into a composition for human administration. Thus, it is clear that the elected and non-elected claims relate to a single general inventive concept under PCT Rule 13.1 and possess the same or corresponding special technical feature under PCT Rule 13.2. Therefore, Applicants respectfully request that the non-elected claims be rejoined with the elected claims for examination.

Although the rejection of claims 13, 16, 30 and 31 under 35 USC § 101 has been withdrawn for the reasons noted in the Official Action dated June 22, 2001, Applicants also wish to bring the following to the Examiner's attention.

Applicants have enclosed for the Examiner's review and consideration two published International Patent Applications of Synaptica Limited which clearly support the specific and

substantial credible asserted utility of the Synaptica peptide (and functional analogues thereof which retain the same calcium channel modulatory function in the absence of cholinesterase activity) as a tool in developing therapeutics and diagnostic systems for neurodegenerative diseases, especially Alzheimer's disease. WO 01/49107 discloses that injection of the Synaptica peptide into rat brains can produce attentional deficit reminiscent of Alzheimer's disease. WO 01/73446 describes studies showing that the ability of Synaptica peptide to modulate induced calcium flux into neurons is mediated by binding to an allosteric site on the alpha 7 nicotinic receptor.

Thus, in light of these applications, Applicants believe that in addition to the reasons noted in the June 22, 2001 Action, the claimed peptide of the present invention also possesses the specific and substantial credible asserted utility noted above.

With regard to the rejection of claims 13, 16, 30, 31 and 33 under 35 USC § 112, first paragraph, this rejection is deemed to be untenable and is thus respectfully traversed.

The Examiner has argued in her rejection that the specification does not enable one skilled in the art to make and use the structural variants set forth in the claims. Specifically, the Examiner believes that the specification fails to teach the skilled artisan those structural determinants which provide the functional activity of calcium ion influx. However, as argued in Applicants' response of February 5, 2001 and herein below, the specification does teach one skilled in the art how to obtain functional variants as defined in the claims.

As recited in claim 13 of the present invention, the claimed functional variants must (i) comprise at least 6 amino acid residues, (ii) have at least 70% homology with all of the peptide of

SEQ. ID No. 1 and (iii) retains the calcium channel modulatory function of the peptide of SEQ. ID No.1 and have no cholinesterase activity. The claim clearly defines the present invention in both a structural and a readily testable functional manner. For instance, Example 3 of the specification illustrates, as an example, an experimental system whereby compliance with the functional requirement of claim 13 may be verified ***for any such variant***. Other experimental systems may also be employed on the basis of the disclosure of the specification. Obtaining species variants or allelic variants of a known DNA sequence is a very different matter from obtaining functional variants of a known biologically active peptide of 14 residues in length.

To further prosecution and to more particularly define the structural limitations of claim 13, Applicants have amended claim 13 to define the functional variants as having at least 70% homology with all of the peptide of SEQ. ID No. 1 and no cholinesterase activity. Such language clarifies that the presently claimed peptide are directed to ***fragments of AChE or variants thereof*** which has a high degree of homology (70%) in comparison to the complete peptide of SEQ. ID no. 1 and retains the calcium channel modulatory function of the peptide of SEQ. ID No.1.

Hence, Applicants strongly believe that given the limitations in the claims and the teachings of the specification, an artisan would now only require at most routine experimentation to determine the functional variants of the Synaptica Peptide. As a result, Applicants respectfully submit that this rejection cannot be sustained and should be withdrawn.

With regard to the rejections of claims 13 and 16 under 35 USC § 102(b) as being anticipated by Serres et al. or Moran et al., these rejections are deemed to be untenable and are thus respectfully traversed.

As stated in Applicants' previous response, under U.S. case law, to constitute anticipation of the claimed invention, a single prior art reference must disclose each and every material element of the claim. Here, in this case, neither of the references cited by the Examiner teaches the Synaptica Peptide or variants thereof as encompassed by amended claim 13.

The present rejections based on the cited journal papers of de Serres et al. and Moràn et al. rely on the incorrect technical assumptions that the functional limitations in claim 13 are not effective to exclude the C-terminal T40 peptide fragment of AChE or even whole AChE. With the insertion of the phrase "no cholinesterase activity", claim 13, as amended, now makes even clearer that whole AChE cannot be regarded as a functional variant of the claimed Synaptica peptide since it is a cholinesterase. In addition, since Synaptica Peptide is a non-enzymatic fragment from within the T40 tail of T-form AChE, which exhibit properties (calcium channel modulation) not exhibited by the whole T40 fragment, it is also clear that the C-terminal T40 peptide fragment of AChE is not a function variant of the claimed Synaptica Peptide.

It is also important to consider that the functional requirement specified in amended claim l3 (activity as a calcium channel modulator) **is not shared** by the whole AChE. As indicated on page 4, lines 24-25, of the specification, the claimed Synaptica Peptide corresponds to residues 535-548 of human AchE and not the whole AChE. This region is a part of the C-terminal tail region of AChE believed to be responsible for holding monomers of the enzyme in tetrameric form. Whole acetylcholinesterase is a large enzyme and would not normally be classified as a peptide.

Applicants have submitted a Declaration by Dr. Westwell demonstrating that AChE do not possess the calcium channel modulatory function required in the claims. Dr. Westwell's Declaration clearly establishes that the processing of AChE as well as the T40 peptide is essential to reveal the calcium channel modulatory function embodied by the claimed Synaptica peptide and that this function is mediated by the targeting of an allosteric site on the alpha 7 nicotinic receptor. Complete AChE has no such effect on the same receptors. Thus, it is clear from the enclosed Declaration that the functional requirements (having a calcium channel modulatory function and no cholinesterase activity) in amended claim 13 excludes whole AChE.

Further, as stated in Applicants' response of February 5, 2001, the first peptide mentioned on page 281 of the de Serres et al. reference overlaps with only the first 4 amino acid residues of the β-APP fragment specified in paragraph 3 on page 5 of the subject application (SEQ. ID No. 2) and the first three amino acid residues of Synaptica peptide (SEQ. ID No. 1). It is to be noted, however, that it has a far longer N-terminal portion which is completely unrelated and irrelevant to SEQ. ID No. 1. The second peptide mentioned on page 281 of the de Serres et al. reference ("de Serres peptide 2") overlaps with the final five amino acid residues of SEQ. ID No. 2. Only two of those amino acid residues (VH) overlap with SEQ. ID No. 1 in the alignment given in Figure 1. The de Serres peptide 2 contains far more sequence which is completely irrelevant to SEQ. ID No. 1. Even SEQ ID No. 2 itself, which has far more homology with SEQ ID No. 1 than either of the peptide substrates mentioned in de Serres et al. does not exhibit the calcium channel modulatory function of SEQ ID No. 1 (*see lines 23 to 24 on page 5 of the specification*).

With regard to the Moran et al. reference, this reference contains no disclosure which teaches or suggests any peptide fragment of AChE encompassed by the limitations of claim 13. The only peptide referred to in this reference is an N-terminal fragment of β-amyloid protein which was used to obtain a monoclonal antibody. The monoclonal antibody was used to demonstrate colocalization of protein recognized by the monoclonal antibody with acetylcholinesterase and butrylcholineserase in brain section plaques. Such studies do not disclose the peptide as now claimed or assist in any way the selection of such a peptide from a complete AChE protein sequence.

Thus, since de Serres et al. and Moràn et al. fails to teach or suggest all the limitations of amended claim 13, these rejections under 35 USC § 102(b) cannot be sustained and should be withdrawn.

With regard to the written description rejection of claims 13, 16, 30, 31 and 33 under 35 USC § 112, first paragraph, this rejection is deemed to be untenable and is thus, respectfully traversed.

Under the new written description guidelines, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, formulas, and functions that fully set forth the claimed invention.

As stated earlier, the Applicants have defined the variants of the Synaptica Peptide by structure ("comprising at least 6 amino acid residues, and having at least 70% homology with all of the peptide of SEQ ID No. 1") and by function ("retaining the calcium channel modulatory function of the peptide of SEQ ID No. 1 and having no cholinesterase activity"). Applicants have also provided in the specification, as an example, an experiment to test for such function (*see Example 3 of the specification*), and how such function is observed and determined ("*when said peptide is contacted with an organotypic culture of neurons of the substantia nigra under conditions wherein calcium influx is induced*").

Under the new written description guidelines, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. The structural and functional description of the variants of the Synaptica Peptide was clearly set forth in the specification and original claims as of the filing date (*see page 5 of the specification and Examples*).

As made clear from the Declaration of Dr. Westwell, the functional limitation excludes for example, very long C-terminal fragments of AChE , e.g. the T40 peptide or longer, and full length AChE. Hence, the peptides encompassed by the claims are clearly within the possession of the inventors. The Examiner's current written description rejection is based on an interpretation of a far broader scope which encompasses proteins which do not possess or satisfy all the limitations of the claims.

It should be noted that the Applicants are not required under U.S. practice to provide evidence for every possible variant of the peptide which falls within the scope of the claims. It

would be evident to a person skilled in protein chemistry that functional variants of the claimed Synaptica peptide were in the possession of the inventors at the time the application was filed based on the structural and functional limitation of the claims.

The Declaration of Dr. Westwell provides evidence, for example, that the biotinylated and amidated version of the claimed Synaptica peptide functions as a calcium channel modulator and the identification of further functional variants can be achieved, for example, by applying a simple cell culture test of the type referred to above and described in Example 3 of the specification. Based on this supportive evidence, it is clear that the peptides encompassed by the limitations of the claims, in combination with the teachings of the specification and the relevant common general knowledge in the art, are within the possession of the inventors at the time the application was filed.

Thus, in view of the above, Applicants submit that the written description rejection under 35 USC § 112, first paragraph, can not be sustain and should be withdrawn.

With regard to the rejection of claims 13, 16 and 30-33 under 35 USC § 112, second paragraph, this rejection is deemed to be overcome by the amendments to claim 13 and the following comments.

Applicants have inserted in claim 13 the phrase "*said peptide having a calcium channel modulatory function*" to provide antecedent basis for the claim limitation of "calcium channel modulatory function".

Further, Applicants strongly believe that the phrase *"said calcium channel modulatory function*" when read in light of the teachings of the specification and in particular, Example 3,

clearly allows the skilled artisan to discern the metes and bounds of this functional limitation. As emphasized in Applicants' last response, the experimental set up described in Example 3 does, for example, exemplify a simple cultured cell system which may be used to identify peptide functional analogues of the claimed Synaptica peptide. These will be peptides which like Synaptica peptide lack the cholinesterase enzymic site of AChE but share the ability of Synaptica peptide to modulate induced calcium flux into the cells.

Thus, in view of the amendments to claim 13 and the arguments above, Applicants believe that this rejection can no longer be sustained and must be withdrawn.

With regard to the rejection of claims 13, 16, 30, 31 and 33 under 35 USC § 102(e) as anticipated by Soreq et al. (USP 5,932,780), this rejection is deemed to be untenable and is thus respectfully traversed.

This new rejection based on the C-terminal "Exon 6" peptides of AchE (SEQ ID Nos: 7, 8 and 25) disclosed in Soreq et al. relies on the assumption that such peptides are capable of exhibiting calcium channel modulatory function in the same way as the claimed Synaptica peptide. This assumption is based on simple fact that the C-terminal T40 peptide fragment of AChE (the product of Exon 6 of AChE) contains the presently claimed Synaptica peptide. However, as evidenced in Dr. Westwell's Declaration, this assumption is false. Further, as also noted in the Declaration, it has been found that the T40 peptide and the claimed Synaptica peptide have very different structures. Consequently, the Soreq et al. Patent is correct to be silent with respect to the calcium channel modulatory function since no such function is present in the C-terminal "Exon 6" peptides of AchE (SEQ ID Nos: 7, 8 and 25).

It is important for the Examiner to recognize that the whole AChE or T40 peptide must be processed to produce the biological activity (calcium channel modulation) exhibited by the claimed Synaptica peptide. Animal model data as referred to in Patent Application WO 01/49107 (see copy appended as Exhibit 2 to the Westwell Declaration) supports that such processing underlies linkage of AChE to neurodegenerative disease. Hence, far longer fragments of AChE, in particular, the complete T40 peptide or longer, are clearly not within the scope of the claims since they do not retain the required biological function of calcium channel modulation.

Thus, since the cited Soreq et al. patent fails to teach a peptide encompassed by the claims, this rejection under 35 USC §102(e) must be withdrawn in light of the enclosed Declaration.

With regard to the rejection of claim 33 under 35 USC § 102(b) as being anticipated by Dagerlind et al., Neuroscience, 62(1):217-239, 1994, this rejection is deemed to be untenable and is thus respectfully traversed.

For the reasons noted above, this rejection also cannot be sustained since Dagerlind et al. do not teach the peptides encompassed in claim 13 for use in making antibodies. Hence, the monoclonal antibodies of Dagerlind et al. which recognize different epitopes of AChE does not recognize a particular fragment of AChE which shows calcium channel modulatory function in the absence of cholinesterase activity.

Thus, since the antibodies of Dagerlind et al. is clearly distinguishable from that of claim 33, this rejection cannot be sustained and should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

Susan A. GREENFIELD et al.

By: _____

Lee Cheng
Registration No. 40,949
Attorney for Applicants

LC/gtg
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 8, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 13 has been amended as follows:

13. (Twice amended) An isolated peptide selected from the group consisting of (a) the peptide of SEQ ID No. 1, said peptide having a calcium channel modulatory function, and (b) functional variants thereof, said functional variants (i) comprising at least 6 amino acid residues, (ii) having at least 70% homology with [part or] all of the peptide of SEQ. ID No. 1 and (iii) retaining [the] said calcium channel modulatory function of the peptide of SEQ. ID No.1 and having no cholinesterase activity.

Introduction of excess of high affinity site will reduce the biological effect.

d) Block the receptor with an antagonist, e.g. design an analogue that binds the receptor, competes with endogenous peptide, but does not raise calcium levels. In an experimental system showing binding and calcium ion signals, it will be possible to assay for a class of compounds that bind the receptor, compete with the peptide ligand, but do not themselves activate the receptor.

e) Uncouple the receptor from the cellular response, e.g. by preventing ligand binding to the receptor from causing cellular response by blocking a second messenger that is preferably unique to the system.

EXAMPLE 2

The 14-mer AChE peptide, the corresponding 14-mer human BuChE peptide (AGFHRWNNYMMDWK) and the 16-mer β-amyloid peptide were synthesised and used in studies to assess their biological activity, with the summarised results given in Examples 3 to 7

Evidence for alpha helical structure of the AChE 14-mer peptide

The inventors inferred from the known alpha helical structure of the region of the beta amyloid peptide homologous to the AChE 14-mer peptide that the peptide was likely to adopt a helical conformation. This is significant because it is only in this helical conformation that the residues conserved between the acetylcholinesterase (AChE) sequence and the amyloid precursor protein (APP) sequence are brought together to form a patch on one side of the peptide; it was suggested that this striking conservation exists because this patch is the interaction surface with a second component, probably a cell surface receptor. Far-UV circular dichroism spectra have been obtained. The solvent used is 95% trifluoroethanol; this is a standard condition for the determination of conformation in small peptides, and is the condition used for published

determination of β-amyloid peptide structure. The results clearly show that the AChE 14-mer peptide adopts a helical conformation under conditions in which a related peptide derived from the homologous region of APP is also helical. These experiments also show that the peptide from the homologous region of butyrylcholinesterase (BuChE) adopts a random coil configuration under these conditions. This is significant since BuChE is regarded as a negative control because this enzyme lacks the non-cholinergic trophic effects of AChE.

EXAMPLE 3

(i) Electrophysiological studies

These experiments are performed on slices of guinea-pig midbrain maintained *in vitro*. Intracellular recordings are made from a rostral population of neurons in the substantia nigra under current clamp conditions. All results listed below are obtained in the presence of the sodium channel blocker tetrodotoxin. In order to facilitate visualisation of calcium-mediated potentials triggered by activation of NMDA receptors, all experiments are performed in magnesium-free perfusate. Under these conditions, results to date indicate:

(a) In 11 neurons, in concentrations ranging from 10^{-7}M to 10^{-6}M, the peptide fragment derived from AChE has a selective and reversible action reminiscent of the actions of AChE itself, i.e. with lower doses/less sensitive situations there is an enhanced calcium influx. This effect is followed by, in sustained applications/stronger doses/more sensitive neurons, a marked reduction in the calcium potentials.

(b) Under conditions where AChE is normally effective and under magnesium-free conditions, the comparable BuChE fragment appears without corresponding effect (n=3), and the analogous fragment of β-amyloid also appears ineffective (n=4). However, a synergism between the peptide derived from AChE and this fragment of β-amyloid is reflected